Reply: Atherosclerosis and Vascular Cognitive Impairment Neuropathological Guidelines (VCING)

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Sir,

Our aim in developing the Vascular Cognitive Impairment Neuropathological Guidelines (VCING) was to establish criteria that we could show to be highly reproducible between neuropathologists in different centres, for post-mortem assessment of the likelihood that cognitive impairment was attributable to cerebrovascular pathology. To ensure reproducibility, we performed blinded post-mortem assessment of sections of brain tissue that were circulated to nine neuropathologists in centres across the UK. The advantage of this approach was that it enabled us to develop a protocol that can easily and reliably be applied in centres other than those participating in the VCING project. However, as noted by Oveisgharan and Hachinski (Oveisgharan and Hachinski, 2016), our approach did impose certain practical constraints on the scope and scale of the study. In particular, it restricted our assessment to variables that could be evaluated by

examination of histological sections, and limited the number of cases that it was practicable to assess (as each case required the assessment of 151 separate variables by 9 neuropathologists).

We agree that other studies have found moderate to severe atherosclerosis of the carotid arteries or circle of Willis to be associated not only with microinfarcts, lacunar infarcts and larger cerebral infarcts (Arvanitakis *et al.*, 2016b; Dolan *et al.*, 2010; Reed *et al.*, 1994; Reed *et al.*, 1988) but also dementia (Arvanitakis *et al.*, 2016a; Dolan *et al.*, 2010). Although atherosclerosis of the basal arteries was, for the stated reasons, not one of the variables included in our modelling of the risk of cognitive impairment, we have now reanalysed the data after incorporating information on circle of Willis atherosclerosis (recorded by the examining neuropathologist for all but 3 of the cases) in our predictive models. In our cohort, we find moderate/severe atherosclerosis to be a significant predictor of MMSE < 27 ($p = 0.02$), even in the presence of the other three most strongly predictive covariates (moderate/severe occipital leptomeningeal cerebral amyloid angiopathy, moderate/severe arteriolosclerosis in occipital white matter, and at least one large infarct), but not to predict a clinical diagnosis of dementia, MMSE < 24, or cognitive impairment, the last of these being the primary outcome measure in our study.

There is evidence that atherosclerosis of the circle of Willis may be a risk factor for Alzheimer's disease (Beach *et al.*, 2007; Honig *et al.*, 2005; Roher *et al.*, 2003; Yarchoan *et al.*, 2012) and, as noted above, it is associated with cerebral infarcts that are themselves a risk factor for vascular cognitive impairment. Dolan *et al*. (2010) found that intracranial atherosclerosis was associated with an increased risk of dementia that was independent of Alzheimer's disease pathology or cerebral infarcts in the Baltimore Longitudinal Study of Aging cohort, but it remains to be established whether circle of Willis atherosclerosis is truly an independent determinant of vascular cognitive impairment. We suggest that this merits further research, and would encourage studies to assess the reproducibility of the VCING model in much larger cohorts, preferably with standardised prospective collection of cognitive data.

Funding

Supported by a grant from the Alzheimer’s Society and a Network Co-operation grant from Alzheimer’s Research UK. The Newcastle Brain Tissue Resource and the Oxford Brain Bank are part of the Brains for Dementia Research program, jointly funded by Alzheimer’s Research UK and Alzheimer’s Society, and are supported by the Medical Research Council. During the course of the study M.E. received financial support from the NIHR, via the Oxford Biomedical Research Centre.

References

Arvanitakis Z, Capuano AW, Leurgans SE, Bennett DA, Schneider JA. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. Lancet Neurol 2016a; 15: 934-43.

Arvanitakis Z, Capuano AW, Leurgans SE, Buchman AS, Bennett DA, Schneider JA. The relationship of cerebral vessel pathology to brain microinfarcts. Brain Pathol 2016b; 10.1111/bpa.12365.

Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, et al. Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 2007; 113: 13-21.

Dolan H, Crain B, Troncoso J, Resnick SM, Zonderman AB, Obrien RJ. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. Ann Neurol 2010; 68: 231-40.

Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology 2005; 64: 494-500.

Oveisgharan S, Hachinski V. Atherosclerosis and vascular cognitive impairment neuropathological guideline. Brain 2016; ???: ???-???

Reed D, Jacobs DR, Jr., Hayashi T, Konishi M, Nelson J, Iso H, et al. A comparison of lesions in small intracerebral arteries among Japanese men in Hawaii and Japan. Stroke 1994; 25: 60-5.

Reed DM, Resch JA, Hayashi T, MacLean C, Yano K. A prospective study of cerebral artery atherosclerosis. Stroke 1988; 19: 820-5.

Roher AE, Esh C, Kokjohn TA, Kalback W, Luehrs DC, Seward JD, et al. Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. Arterioscler Thromb Vasc Biol 2003; 23: 2055-62.

Yarchoan M, Xie SX, Kling MA, Toledo JB, Wolk DA, Lee EB, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. Brain 2012; 135: 3749-56.